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DOSE RESPONSE STUDIES. I. SOME DESIGN CONSIDERATIONS

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Abstract

A critical aspect of biomedical research is the characterization of the dose response relationship of a compound. This is true in laboratory experiments and clinical trials and pertains to efficacy, safety, and the resulting benefit/risk ratio. Presented here is Part I of this article, which deals with some clinical trial design issues surrounding dose response studies. Some additional comments are made about trials for identifying the minimum effective dose, randomized concentration controlled trials, and the use of one-sided hypotheses in designing such trials. Part II is a separate paper reviewing some analysis strategies for dose response studies.

1. Introduction

Understanding the dose response relationship of a compound is a fundamental aspect of research; indeed, it may be the central issue. This is true whether studying a new drug, assessing the effect of environmental toxins, or eval-

uating the hazard from industrial chemicals. In the pharmaceutical industry classical dose response studies are used in pharmacology, toxicology, and clinical research. Dose response relationships and the issues surrounding their study also can play an important role in pharmacokinetics (studying dose proportionality), assay validation, and concentration response for *in vitro* studies.

In studying the dose response relationship of a new drug, several fundamental questions that dictate design and analysis strategies need to be answered. These questions are:

1. Is there any evidence of a drug effect?
2. What doses exhibit a response different from the control response?
3. What is the nature of the dose response relationship?
4. What is the optimal dose?

Each question in this list becomes increasingly specific in its quest for information about the drug. Early in the drug development process, one may want only to know, "Is there any evidence of a drug effect?" so that one can make go/no-go decisions about future development. As progress is made through drug development, one may wish to answer the final question, "What is the optimal dose?"

These questions about the dose response relationship apply to efficacy, safety, and the benefit/risk ratio. While typical pharmaceutical clinical trials are focused on efficacy responses, as larger trials are completed and data bases built on hundreds or thousands of patients, the dose response relationship with regard to safety can also be assessed. With efficacy and safety data in hand, the benefit/risk ratio can be evaluated. This paper will deal with some trial design issues and considerations. It is not meant to be an exhaustive review of all trial designs, but is meant to review issues and designs relevant to drug development. A subsequent paper will focus on analysis and interpretation of data collected from dose response trials.

2. Some Experimental Designs

2.1 Parallel Designs

The most common and straightforward design is the placebo-controlled, randomized, parallel dose response study. In this study design, patients are randomly allocated to one of several active dose groups or placebo. This design is most popular since the only difference between treatment groups is the dose of the experimental compound, allowing for straightforward interpretation of the results of such a trial. It is also important that the study include a placebo group since a significant trend in response with increasing dose in the absence of placebo is not necessarily evidence of a drug effect (Fig. 1).

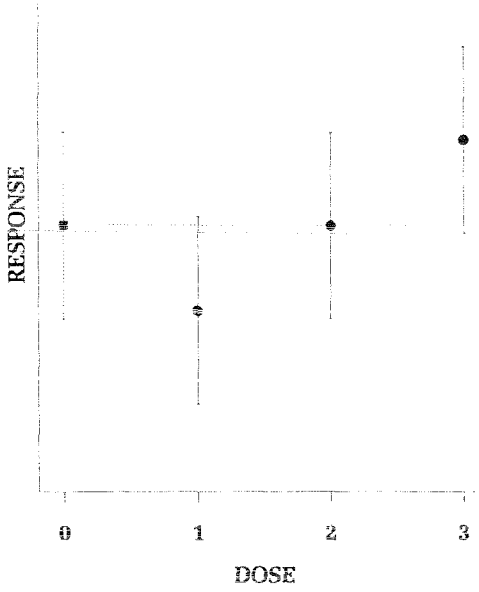

Figure 1. Dose response with and without placebo control group.

In Figure 1, if the placebo response were absent, one might conclude there is a significant dose effect because response is increasing with dose. However, when the "trend" in response with increasing dose is taken in light of the placebo response, it may be doubtful that there is any drug effect.

There are some exceptions to this principle of needing a placebo group to assess the significance of dose response. In some cases, the historical placebo response is nil or nearly nil (e.g., spontaneous cures of serious infections such as endocarditis, the absence of nausea and vomiting following highly emetogenic chemotherapy, or chronic asthma), and therefore, a concurrent placebo group is not necessary. Furthermore, from a safety standpoint, there may be instances where a single serious adverse event is evidence of a toxic drug effect in the absence of placebo.

In many instances, clinicians like to use dose titration to assess the drug effect. This is appealing early in drug development programs since patient safety is generally of greater concern. In these trials patients can be started at low doses, and depending on their response, doses can be increased gradually to achieve a suitable dose for the patient. The assessment of an individual patient's dose response is satisfying clinically and may require fewer patients to assess the drug effect since within-patient variability is used. The disadvantage of titration studies is that dose and time effects cannot be completely separated. Since efficacy and adverse events may have a time-

dependent component, the real drug effect may be obscured. One way to help assess the drug effect is to have a concurrent placebo group. This allows for an assessment of the overall drug effect, but assessment of individual dose effects remains confounded with time. Titration studies are most appropriate when the ultimate use of the drug will be in some titration scheme. A variety of dose escalation and titration schemes for phase I and phase IIa trials are reviewed by Rodda *et al.* (1).

One possible compromise between doing a parallel design, which statisticians tend to prefer, and titration designs, which clinicians tend to prefer, is to do a parallel study in which the parallel treatment groups are actually various titration schemes. That is, patients are randomized to distinct titration regimens. One might even choose a factorial arrangement in which, for example, two dose step sizes are studied with two time intervals between steps (5- and 10-mg dose steps at 1- or 2-week intervals). This allows for independent comparisons of titration/dosing regimens; however, comparison of individual doses is not always possible.

2.2 *Crossover Designs*

The disadvantage of a parallel dose response trial is that the precision of the inference is driven by between-subject variability, which usually requires greater sample sizes to increase the precision of the estimates for drug effect. To overcome this difficulty, crossover trials can be utilized so that within-subject variability, which is most often smaller than between-subject variability, can be used in the inference. The statistical criteria for when a crossover design is better than a parallel design, as well as practical considerations (e.g., the stability of the disease state over time) are well known (2). There are several variations of the crossover study, but two fundamental designs are the completely randomized crossover and the dose escalation crossover.

Typically, Latin squares are used for completely randomized crossover studies. When a very broad dose range is of interest, the use of incomplete crossover studies (Youden squares or balanced incomplete block designs) can be employed effectively. In many clinical settings it is not possible to evaluate clinical endpoints in a short period of time or without some carryover effect. However, in clinical pharmacology studies where surrogate endpoints of efficacy or safety are used in the decision-making process of drug development, such conditions may hold. Furthermore, pharmacokinetic dose proportionality studies or formulation screening bioavailability studies often have many treatments or dose groups. Such studies are well suited to the use of Youden squares or variations on balanced incomplete block designs. If there is a control group or reference formulation that serves as a control, optimal blocks designs for comparisons with control have been developed (3).

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